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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/20
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
FEB 81 M H WEEKS, M J TOPPER

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USAEHA-75-51-0146-81

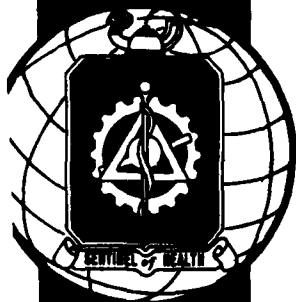
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UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY

ABERDEEN PROVING GROUND, MD 21010

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TOPICAL HAZARD EVALUATION PROGRAM OF
CANDIDATE INSECT REPELLENT A13-37445-a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL
STUDY NO. 75-51-0146-81
SEPTEMBER 1978 - NOVEMBER 1980

Mr. H. W. ...
Mr. J. I. ...

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A hazard evaluation of candidate insect repellent AI3-37445-a was performed by means of laboratory studies using rats, rabbits, and guinea pigs. The technical grade compound caused mild eye irritation, but no skin irritation or photochemical irritation in rabbits, no sensitization reactions in guinea pigs and did not demonstrate an acute ingestion hazard. It is recommended that AI3-37445-a, US Department of Agriculture Proprietary Chemical, be approved for further testing as a candidate insect repellent.		

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

Mr. Weeks/mhb/AUTOVON
584-3980

11 FEB 1981

HSE-LT-T/WP

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent
AI3-37445-a, US Department of Agriculture Proprietary Chemical,
Study No. 75-51-0146-81, September 1978 - November 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

A hazard evaluation of candidate insect repellent AI3-37445-a was performed by means of laboratory studies using rats, rabbits, and guinea pigs. The technical grade compound caused mild eye irritation, but no skin or photochemical irritation in rabbits, no sensitization reactions in guinea pigs, and did not demonstrate an acute ingestion hazard. It is recommended that AI3-37445-a, US Department of Agriculture Proprietary Chemical, be approved for further testing as a candidate insect repellent.

FOR THE COMMANDER:

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John F. Mazur
JOHN F. MAZUR
MAJ, MSC
Director, Laboratory Services

CF:
HQDA (DASG-PSP)
Cdr, HSC (HSPA-P)
Dir, Advisory Cen on Tox, NRC
Comdt, AHS (HSA-IPM)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Rgn

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

TOPICAL HAZARD EVALUATION PROGRAM OF
CANDIDATE INSECT REPELLENT AI3-37445-a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL
STUDY NO. 75-51-0146-81
SEPTEMBER 1978 - NOVEMBER 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, FL, 13 September 1978.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of candidate insect repellent AI3-37445-a.

4. SUMMARY OF FINDINGS. Hazard evaluation of the candidate repellent AI3-37445-a, US Department of Agriculture (USDA) Proprietary Chemical, was conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:*†

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study No. 75-51-0146-81, Sep 78 - Nov 80

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Compound AI3-37445-a produced mild irritation of the skin in only one rabbit at 24 hours but no skin irritation in the other rabbits	USAEHA Category I (ref Appendix A)
0.5 mL technical grade compound applied to each of six rabbits.	Details of study are found in Appendix B.	
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 mL technical grade compound to one eye of each of six New Zealand White rabbits.	Compound AI3-37445-a produced mild injury to the iris and conjunctivae in four of six rabbits with signs reversing to normal at 7 days. Details of study are found in Appendix C.	USAEHA Category C (ref Appendix A)
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male) - no diluent	ALD >4300 mg/kg	Presents little lethal hazard from acute accidental ingestion.

Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single 0.05 mL application of a 25-percent (w/v) solution of AI3-37445-a and a 10-percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	A 25-percent solution of AI3-37445-a in ethanol did not cause a photochemical irritation reaction under test conditions. Ethanol solutions of AI3-37445-a caused a moderate erythematous and edematous reaction on both non-UV and UV skin sites.	Compound AI3-37445-a did not cause a photochemical irritation reaction under test conditions and is not expected to cause a photochemical irritation in humans.
<u>Control</u>		
Following UV exposures of the rabbits, 0.05 mL of test compound, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas. Details of study are found in Appendix D.	Ethanol solutions of this compound may cause moderate skin irritation in sensitive individuals. Persons experiencing this reaction should wash off the solution as soon as possible.

Test	Results	Interpretation
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injections of 0.1 mL of a 0.1-percent suspension (w/v) of AI3-37445-a or of dinitro-chlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs were given 10 sensitizing doses over a 3-week period. After 2 weeks rest, they were challenged with ID injections of test compound.	Challenge doses of test compound did not produce a sensitization reaction.	Compound AI3-37445-a did not produce sensitization reaction under test conditions and is not expected to cause sensitization reactions in man.
Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB produced a marked sensitization reaction in 10 out of 10 guinea pigs. Details of study are found in Appendix E	DNCB produced a marked reaction, indicating the guinea pigs respond to strong sensitizing agents.

* A known skin sensitizer

Study No. 75-51-0146-81, Sep 78 - Nov 80

5. CONCLUSION. The candidate insect repellent AI3-37445-a has a potential for causing some slight eye irritation, but presents no acute hazard from skin or photochemical irritation, from sensitization reactions or from acute ingestion. Moderate irritation may result from contact with ethanol solutions of AI3-37445-a.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37445-a, USDA Proprietary Chemical, be approved for further testing as a candidate insect repellent. The compound should be used with caution around the eyes. Persons experiencing irritation when working with ethanol solutions of AI3-37445-a should wash the site with copious amounts of water.



MAURICE H. WEEKS
Chief, Toxicity Evaluation Branch
Toxicology Division



MICHAEL J. TOPPER, DVM
CPT, VC
General Veterinary Officer
Toxicology Division

APPROVED:



ARTHUR H. MCCREESH, Ph.D.
Chief, Toxicology Division

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

APPENDIX B

COMPOUND: AI3-37445-a USDA Proprietary Chemical										USAEHA STUDY NO. 75-51-0146-81									
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS					USAEHATOXICITY CATEGORY I					CONDITIONS - 0.5 mL technical grade compound applied for 24 hours to intact or to abraded skin.									
	Time of Observation (Hours)	Response Rabbit No.								Mean Score	Comments								
		477	478	479	480	481	482												
<u>Erythema & Eschar</u>																			
Intact Skin	24	0		2		0			0.7										
Intact Skin	72	0		0		0			0										
Abraded Skin	24		0		0		0		0										
Abraded Skin	72		0		0		0		0										
								Subtotal	0.7										
<u>Edema Formulation</u>																			
Intact Skin	24	0		1		0			0.3										
Intact Skin	72	0		0		0			0										
Abraded Skin	24		0		0		0		0										
Abraded Skin	72		0		0		0		0										
								Subtotal	0.3										
								Total	1.0										

APPENDIX C

COMPOUND: AI3-37445-a			USDA Proprietary Chemical			USAEHA STUDY NO. 75-51-0146-81						
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS			USAEHATOXICITY CATEGORY C			CONDITIONS - 0.1 mL technical grade material applied to one eye of each rabbit.						
Time of Reading	Hrs-Days	Structure	Scores								Mean Score	Comments
			Rabbit No.									
			447	448	449	450	451	452				
24		cornea	1	0	0	1	1	1	0.7			
		iris	1	0	0	1	1	1	0.7			
		conjunctivae	1	0	0	3	4	4	2.0			
48		cornea	1	0	0	1	1	1	0.7			
		iris	1	0	0	0	0	0	0.2			
		conjunctivae	4	0	0	2	2	2	1.7			
72		cornea	1	0	0	0	1	0	0.3			
		iris	0	0	0	0	0	0	0			
		conjunctivae	0	0	0	0	0	0	0			
7-days		cornea	0	0	0	0	0	0	0			
		iris	0	0	0	0	0	0	0			
		conjunctivae	0	0	0	0	0	0	0			

USAEHA FORM 26-2, 21 JUN 79 (HSE-LT)

APPENDIX D

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

COMPOUND: AI3-37445, a USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0146-80				
COMMENTS: Test chemical did not demonstrate photo irritant properties, but the 25% ethanol solution was moderately irritating with and without UV irradiation.						
PROCEDURE:						
Observation Time	MEAN SKIN IRRITATION SCORE					
	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure	
	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	10	9	10	7	11	8
48 Hours	10	5	10	3	10	4
72 Hours	11	4	9	4	11	3
TOTAL	32	18	29	14	32	15
Mean Irritant Responses						
Net Score	50		43		47	
					8	

ADHA Form 6, 1 Feb 81 (031-11)

APPENDIX E

COMPOUND: AI3-37445-a		USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0146-81			
GUINEA PIG SENSITIZATION Test Substance: USDA Proprietary Chemical test concentration 0.1%.							
MALE							
HARTLEY STRAIN							
Identify: AI3-37445-a							
Positive Control: DNCB test concentration 0.1%.							
Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores				Comments
	Initial	Final	Diluent		Test Compound		
			Initial	Final	Initial	Final	
Test Compound	503	737	0	0	1.2	1.6	Test chemical did not demonstrate a sensitization potential under test conditions.
Positive Control	491	736	0	0	19	356	
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores				Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing
	Initial	Final	Diluent		Test Compound		
			Initial	Final	Initial	Final	
Test Compound	--	--	0	0	0.4	0.4	
Positive Control	--	--	0	0	5.4	266	

